SHORT TESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

CLINICAL EPIDEMIOLGICAL EXAMINATION OF RENAL TRANSPLANTATION

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The Examination takes place at the Conference Room in Department of Preventive Medicine, Faculty of Public Health , University of Debrecen at 11 a.m., December 21, 2018

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The PhD defense takes place at the Lecture Hall of BIdg. A, Department of Intenal Medicine, Faculty of Medicine, University of Debrecen at 1:00 p.m., 21th December, 2018.

1. Introduction

Major epidemiological studies from recent years clearly indicate that chronic renal disease has become a very significant public health challenge globally, affecting 10 to 14% of the population in developed countries and causing substantial expenditures. More than a half of patients have a glomerular filtration rate (GFR) of less than 60 mL/min; however, no more than 1 to 2% are in the highest severity group with end stage renal failure. This is explained by a highly accelerated atherosclerosis, owing to which the majority of patients die before renal replacement therapy could be started. Patients started on dialysis as late as in stage 5 chronic kidney disease face the highest levels of mortality, with a cause structure primarily dominated by deaths from severe cardiovascular morbidity. It has been known since an analysis by Foley that cardiac mortality in dialysis patients is 10 to 20 times greater than in the average population. Cardiac mortality may be reduced to as low as a fraction of this level after successful renal transplantation but it still remains at 3 to 5 times above the reference range of the average population. In his studies based on the USRD database, Meier-Kriesche points out that post-transplant mortality as well as kidney graft survival are

correlated with the length of time in ESRD and time spent on the waiting list. The leading causes of death in patients who die with a functional kidney allograft are cardiovascular diseases, which constitute nearly 40% of fatalities. Obesity, diabetes, dyslipidemia, hypertension, immunosuppressive therapy, and smoking are high-risk factors for the development of cardiovascular diseases. Short-term results of renal transplantation improved in the last two decades: one-year survival exceeds 80%, five-year survival is at 77%, and 10-year graft survival is at 56% in Europe. Renal transplantation success is characterized by post-transplant overall survival and quality of life of patients; kidney graft survival is a parameter specific to transplantation. The latter is made up of two components: graft loss may occur due to the recipient's death while the renal function is still intact; and also due to a loss of graft function, which is referred to as mortality-adjusted graft loss and is comprised of re-transplantation and recourse to dialysis. Renal transplantation success factors include surgical technique, occurrence of surgical complications, and the number of previous transplantation attempts in the recipient's medical history. Outcomes with early arterial and venous vascular complications are poor as they lead to renal graft loss in no less than 30 to 50% of cases; however, their effects are negligible since their reported frequency is very low at around

1%. The nature of renal transplantation as an intervention explains the presence of further risk factors: immunosuppression, surgical complications, and infections. The circumstances of the intervention determine what we call the center effect. Highlights of factors on the recipient's side include age, BMI, co-morbidities, delayed graft function (DGF, formerly referred to as ATN – a histological diagnosis), the former one being a condition that requires dialysis in the first few weeks), length of prior dialysis period, smoking, level of education, and social status. Rao et al have concluded that patients older than 70 years have the same relative risk of death on their 125th post-transplant day as dialysis patients on the waiting list; however, cumulative survival in the 4th year after transplantation is 66% compared to 51% in those still on dialysis. In a study by Heldal et al, transplant patients aged over 70 years grafted after the year 2000 had a 5-year survival of 66%, while the figure for those on the waiting list was only 33%. In all age groups, live donor transplantations are likely to produce the most extra years of life gained. Recipients under 55 years of age receiving from SCD (standard criteria donors) have a much greater number of years of life gained, even after lengthy prior dialysis. Life expectancy of patients over 65 is strongly determined by the length of dialysis; these patients benefit from rapid transplantation, even if this makes an ECD

(expanded criteria donor) necessary (ET: senior program). A prognostic index by Molnár et al indicates that when it comes to the clinical selection algorithm, expanded criteria donor kidneys should not be coupled with high-risk recipients; this assessment can be facilitated by consulting www.Txscores.org. COMMIT (Consensus on Managing Modifiable Risk in Transplantation) guidelines report that even though short-term outcomes of renal transplantation improved considerably over the last two decades, long-term survival fails to follow this trend. Kaboré et al recently published a systematic review of publications from the period of 2005 through 2015 summarizing models estimating outcomes of transplanted renal grafts. The definition of graft failure varied across different models, and quite a number of predictors were evaluated including serum creatinine, eGFR, proteinuria, acute rejection, acute tubular necrosis, carotid pulse wave velocity, and the immunosuppression used. Most models determine discrimination performance using receiver operating characteristics (ROC) analysis.

The number of patients returning to dialysis due to chronic damage to the grafted kidney is on the rise. The fifth most common reason behind starting renal replacement therapy is graft loss (DAGL: dialysis after graft loss), which is why the

treatment of this group of patients in clinical practice is important. There is a lack of unified guidelines on optimal timing of renal replacement therapy initiation, type of modality, immunosuppressive therapy withdrawal schemes, transplanted kidney removal, and repeat transplantation. The optimal timing of renal replacement therapy initiation is also unclear. According to a study by Molnár et al, early start of dialysis had no benefit for patients in a poorer condition and in the young age group; however, in women it was associated with increased risk of mortality. As to dialysis modality, the analysis of peritoneal versus hemodialysis survival showed no difference either in the early (<2 years) or the late (>2 years) mortality subgroup. Patients returning to dialysis due to graft loss are characterized by the following: 1. their survival data and quality of life are worse than those of non-transplanted, incident CKD waiting list patients; 2. there is no clear basis for when it is optimal to start dialysis; 3. survival is equal in hemodialysis and peritoneal dialysis.

The classic indications of graftectomy in acute complications are as follows: a. arterial/venous thrombosis; b. treatment-resistant acute rejection; c. graft rupture; d. hemorrhagic complications of biopsy; e. acute septic complications; f. primary non-function graft; g. graft malignancy. In chronic graft failure: a. graft swelling

accompanied by pain upon reduction of immunosuppression; b. hematuria; c. subfebrility, fever; d. ESA resistant anemia, malnutrition-inflammation syndrome (MICS); e. late-onset septic complication; f. recurrent renal disease; g. preparation for third renal Tx. The literature is ambivalent about whether graftectomy is beneficial in DAGL. In early (1 year) kidney graft failure, graftectomy increased the risk of mortality, while in late (>1 year) kidney graft failure, patients undergoing graftectomy had lower risk of mortality and sepsis. Graftectomy patients' level of immunization (anti-HLA PRA) increased, which may reduce the chance of re-transplantation. Ayus et al have concluded that graftectomy was associated with a lower risk of mortality both in early (>1 day, <1 year) and late-onset DAGL. Long-term graft survival is limited partly by the patient's death, and partly by conditions conducive to chronic allograft dysfunction.

Number of studies about cardiovascular screening of high-risk patients are known, but dialysed and transplanted patients are underrepresented in these. The guidelines for cardiovascular risk assessment also vary. Categorizing patients as high, medium, and low risk may help day-to-day care and optimal drug treatment. The Courage study compared the number of angina events occurring post-intervention and under optimal medical therapy. In cases with a GFR above 40, this

produced remarkably good results. The incidence of coronary artery disease in asymptomatic patients with chronic kidney damage is elevated, with at least one coronary artery with a stenosis of greater than 50% being present in 37 to 53% of them. End-stage kidney disease patients are underrepresented in randomized, controlled studies, and receive guideline-approved cardioprotective medications at a suboptimal dose due to an adverse side effect profile (hemorrhagic complications, calciphylaxis). The guidelines of the Hungarian Society of Cardiology and the Hungarian Transplantation Society for the diagnostic workup in coronary artery disease are different. In our work, the 2014 guidelines of the American College of Cardiology and the guidelines on non-cardiac surgery of the European Society of Cardiology were used for waiting list placements.

2. Objectives

2.1. My research objective was to gain understanding of survival and its modifying factors in transplant recipients at UD MHSC. First, I validated an existing Spanish prognostic function on a

group of patients grafted at the UD MHSC Transplantation Center between 1991 and 15-09-2004; the function is used to estimate the risks involved in renal transplantation from a compound effect of various predictive factors. We assessed the calibration and discrimination performance of the function.

2.2. We analyzed the survival of patients returning to dialysis due to graft failure from chronic damage to the transplanted kidney, comparing it to that of hemodialysis recipients with no transplantation. We examined the indications of graftectomy and the histopathology of removed grafts.

We also analyzed the effect of graftectomy on repeat transplantation since no clear verdict exists from literature data so far as to whether or not elective graftectomy is beneficial, since it mainly acts as an immunizer in re-transplantation candidates, which represents an elevated immunological risk, while in those unfit for re-transplantation, it may offer a survival advantage.

2.3. Thirdly the aim of our study was to describe a novel approach of cardiovascular screening and management of dialysis patients evaluated for the transplant waiting list.

3. Subject and methods

3.1 a. Study poplualtion

Based on the published prognostic function, we estimated the 5-year risk of death in 339 cadaver kidney transplant patients (18 years old or older) undergoing a transplant between 1 January 1991 and 15 September 2004 at the Center of Transplantation of the Medical and Health Science Centre University of Debrecen, who were discharged from the hospital and followed until death or 15 September 2009. Second and third kidney recipients and those patients who had received organs other than kidney were excluded from the study. Routine immunosuppression therapy consisted of calcineurin inhibitors (cyclosporinA or tacrolimus), mycophenolate mofetil and steroid. Immunologically highrisk patients received antithymocyte globulin or anti-IL2-R induction therapy.

3.1.b. Data collection

Patient data were collected retrospectively by chart review. The predictors in the prognostic function to be validated were age, serum creatinine level, time on dialysis, vascular calcification, diabetes before transplantation, pretransplant CV disease, left ventricular hypertrophy and acute tubular necrosis. We defined predictors the same way as in the study in which the prognostic function was derived. Left ventricular hypertrophy was determined by echocardiographic or electrocardiographic criteria, hypertension as blood pressure higher than 140/90 mmHg or being on antihypertensive therapy. Vascular calcification was evaluated by preoperative X-ray of the aortoiliac region; pretransplant CV disease included ischemic heart disease, cerebral vascular disease and peripheral vascular disease. Ischemic heart disease was defined as myocardial infarction documented by elevated enzyme levels, with or without electrocardiographic changes or coronary artery revascularization. Cerebral vascular disease was defined as transient ischemic attack or stroke. Peripheral vascular disease was considered if revascularization procedures or amputations had been performed. Follow-up data were obtained annually from the general practitioners of the patients and from the dialysis centers of the 4 Hungarian

counties where the patients lived. The data published about the prognostic function would not have allowed us to perform the validation study. The authors of the paper provided us with the estimated 5-year risk of death in patients with no risk factors; this made it possible to estimate the 5-year risk for each person in our study population.

3.1.c Statistical analysis

We first assessed how well the prognostic function estimated the number of deaths that occurred within 5 years of follow-up. For this purpose, we used 2 methods. First, we compared the predicted 5-year risk of death with the actual 5-year cumulative incidence of death in deciles of predicted risk.

Further, we added up the predicted risks to calculate the expected number of deaths and compared it with the observed

number of deaths in the deciles of the predicted risk. We tested the difference of the observed and the expected numbers of deaths using the Hosmer-Lemeshow test. Secondly, to avoid the (imitation that cumulative incidences can be calculated in only a limited number of groups, preventing direct comparison

of the actual occurrence of death to certain values of the predicted risk, we applied smoother to obtain a nonparametric estimate of the 5-year cumulative incidence of death by robust locally weighted regression. We used a tricube weight function and a bandwidth of 0.5. We plotted this nonparametric estimate of risk - which is based on the actual occurrence of death in each person and influenced by the occurrence of death in persons with similar estimated risk against the estimate of risk provided by the prognostic function.To see how the function would separate participants who died and who survived during follow-up, we calculated the area under the receiver operating characteristic (ROC) curve. A discriminating function yields a wide range of predieted risk and assigns higher predicted risk to participants who will die than to participants who will not die within 5 years. The better the discrimination, the larger is the area under the ROC curve. Additionally, we fitted a Cox proportional hazard model with the same predictors as in the original model which we validated to see the difference in the strength of association between the predictors and the risk of death in our dataset compared with the derivation dataset. Finally we extended the model with some other potential predictors to see whether they can improve the performance of

the model. These predictors were cold ischemia time, HLA match (less than 4 or at least 4), sex and hemoglobin level.

3.2.a Selection and Description of Participants 2.

Demographic data were collected on all patients retrospectively by chart review at baseline. We enrolled 180 patients who started dialysis between 2000-2005, of whom 123 had had no kidney transplantation previously, 12% were waiting-listed for transplantation and 57 were transplanted patients with graft failure (20 of them (35%) were waiting-listed again). In Hungary the proportion of waiting-listed patients is rather low. That derives not only from inadequate patient education but also from the low activity for deceased donor kidney transplants. Transplanted patients received a cadaver kidney between 1991 and 2002 in the Centre of Transplantation, Medical & Health Science Centre, University of Debrecen. Recipients who received organs other than kidneys, and patients younger than 18 years were excluded from the study. Laboratory data obtained at baseline included the following: hemoglobin levels (Hb), GFR, calcium (Ca),

phosphate (P), cholesterol (chol), triglycerides (Tg). Follow-up data were obtained annually from the general practitioners of the patients and also from the dialysis centres of the four Hungarian counties where the patients lived. They were followed till death or till 15 December 2010. Resected kidney transplant specimens were routinely sent to the pathology department for microscopic examination. Specimens were subjected to standard histologic review by a staff pathologist using routine techniques. We used Kaplan-Meier analysis and log-rank test to compare the survival of patients in the HD, in the reHD groups from the start of the dialysis. We adjusted for age and gender in Cox-regression. We performed a similar analysis to compare the survival of patients with graft failure whose graft was removed (43 patients) and those whose graft was not removed (14 patients). Additionally, we compared the clinical characteristics of patients in the HD and reHD groups. We used the two-sample t-test to compare continuous and the χ^2-test to compare categorical variables.

3.3.a Selection and Description of Participants 3.

Detailed clinical and demographic data were collected from the initial transplant assessment. All candidates underwent a

structured medical assessment by a consistent group of transplant physicians before activating the transplant waiting list. This assessment included a medical history, physical examination, lipid profile, fasting glycemia, resting electrocardiogram (ECG) and chest radiograph, and cardiac ultrasound. All 28 study patients were interviewed by a cardiologist to determine the presence of cardiovascular disease and assess the perioperative cardiovascular risk. We put our patients on a wait list between July 2013 and July 2014.

3.3.b Classification of Cardiac Risk

Patients were classified into 3 groups according to their risk, on the basis of the following 3 factors: age, history of diabetes, or ischemic heart disease . High-risk patients (n=8) displayed active ischemic heart disease at age older than 45 years in men and over 55 years in women with a history of diabetes mellitus. Intermediaterisk patients (n=5) of age older than 45 years in men and 55 years in woman had diabetes mellitus or an abnormal baseline ECG. Low-risk patients (n=15) had no risk factors.

3.3.c. Cardiovascular Screening

All patients underwent a clinical assessment that included a history, physical examination, chest radiograph, 12-lead ECG, and transthoracic echocardiogram. An exercise stress test was performed on all low-risk patients with normal ECG; those who tested positive underwent coronary angiography. Myocardial perfusion imaging was performed in patients with intermediate risk or with low risk and abnormal baseline ECG (left bundle branch block, left ventricular hypertrophy, or ST changes, inadequate exercise stress test). Coronary angiograms were performed on all high-risk patients and on patients with positive myocardial perfusion imaging or positive stress tests. Ischemic heart disease was defined as a history of myocardial infarction, CABG, PTCA, or the presence of ischemia on thallium with exercise. Perfusion imaging findings were classified as normal if no perfusion abnormalities were present at rest or with exercise; mild if there was decreased uptake in 2 segments or less; moderate if there was decreased uptake in 3 to 5 segments; and severe if there were abnormalities in more than 5 segments.

3.3.d.Statistics

Descriptive statistics in the form of median values and ranges for interval variables as well as mean values standard

deviation (SD) and frequencies (percentages) for categorical variables were performed using the SPSS 14.0 statistical package (SPSS Inc., Chicago, Ill., United States).

4. Results

4.1. Validation of a porgnostic function in hungarian transplant recipients

The range of the estimated 5-year risk of death had a range of 7%-100%; mean risk was 27.8% and median was 15.3%. Table I shows the observed and the expected number of deaths and the cumulative incidence of death in deciles of the predicted a-year risk of death. The number of subjects in the categories was different, and the first 2 deciles were merged in 1 category because of the many ties. The expected number of deaths (94.7) was much higher than the observed number of 55; the result of the Hosmer-Cemeshow test was significant ($p<0.001$). The function grossly overestimated the risk of death in patients with high risk. Acute tubular necrosis and vascular calcification were more strongly related, and age, serum creatinine level, left ventricular hypertrophy, presence of diabetes mellitus, time on dialysis and pretransplant CV

disease similarly related to the risk of death in the derivation and the validation datasets. Only hemoglobin level had a strong and statistically significant association with the risk of death when it was added to the model (hazard ratio per 10 g/L: 0.92, C', 0.86-0.97; p=O.004). Acute tubular necrosis and vascular calcification were more strongly related, and age, serum creatinine level, left ventricular hypertrophy, presence of diabetes mellitus, time on dialysis and pretransplant CV disease similarly related to the risk of death n the derivation and the validation datasets. Only hemoglobin level had a strong and statistically significant association with the risk of death when it was added to the model (hazard ratio per 10 g/L: 0.92, C', 0.86-0.97; p=O.004).

4.2. Prognosis of dialysed patient after transplant grat failure

The comparison of the HD and the reHD groups revealed several differences. Patients in the reHD group had lower haemoglobin level and higher GFR. The proportion of patients taking statins was larger in the HD group. Patients in the HD group were significantly older. In the crude analysis patients in the reHD group had a much better survival (hazard ratio 0.51,

95% CI: 0.33-0.59). However, after adjustment for age and gender there was no difference in the survival probability of the two groups (hazard ratio reHD versus HD group: 1.09, 95% CI: 0.64-1.87). Two patients committed suicide in the non-graftectomised group. In 43 patients transplanted kidney nephrectomy was performed within 1 year (average: 262 days) after restarting HD. Death within 1-year after readmission to dialysis was 6.97% in the graftectomised and 21.42 % in non-graftectomised group. The indications of the graft nephrectomy were the followings: acute rejection or severe inflammation (in 17 cases), symptoms or signs of severe anaemia (in 12 cases), elective nephrectomies without major symptoms (diuresis less than 500 ml/day) (in 14 cases). Nephrectomised patients had a consistent but statistically not significant survival advantage (crude hazard ratio = 0.50 95 % confidence interval: 0.22-1.12, p=0.09; after adjustment for age and gender hazard ratio: 0.56, 95 % CI: 0.24-1.32, p=0.18). Of the reHD patients 34.8 % were re-transplanted, although none of them had preemptive re-transplant. Our clinical policy for tapering immune suppressive therapy after return to dialysis was the following: (1) antiproliferative drugs (azathioprine, mycophenolate-mofetil, sirolimus) should be the first drugs to be discontinued when irreversible graft failure is established, (2) tapering and withdrawal of

calcineurin inhibitor over a brief period (1-3 weeks) of the graft failure followed a chronic and slow progression, and a longer period (4-8 weeks) if the graft failure followed more acute immunologic events, (3) slow tapering of steroids with possible withdrawal (in a few months) maintaining the same dose of steroid for 1 month, then halving the steroid dose in every month until complete withdrawal. Histologic examination of the resected kidney transplants was available for 37 of the 43 cases. In all 37 cases, there was evidence of chronic rejection characterized by the existence if variable degrees of glomerulitis and tubulitis. Characteristic findings included presence of chronic interstitial mononuclear cell infiltirate (1), subendothelial lymphocytic and monocytic cellular infiltrate (2), intimal vascular fibrosis (3), moderate to severe interstitial fibrosis (4). None of the specimens had viral inclusions or findings suggestive of an infection.

4.3. Cardiovascular screening and management among kidney trasnplant candidates in Hungary

We put 28 new patients on the wait list between July 2013 and July 2014. In total, 46 patients were waitlisted at our center (hemodialysis: 15%, peritoneal dialysis: 50%,

preemptive: 2.3%). The age range of patients was 14 to 73 years (median: 43.6 years). Eight patients in our study population were older than 60 years, 67% were male, and 40% were diabetic, with diabetes mellitus as the leading cause of endstage renal disease. According to our prespecified protocol, 15 (54%) patients were identified as low, 5 (18%) as intermediate, and 8 (28%) as high risk. Four patients (14%) were current smokers. In the low-risk group, we initiated a patient education program involving counseling on regular exercise such as swimming or cycling to improve patients' functional capacity. In the medium-risk group, we opted for medical management, including introduction of beta-blockers, angiotensin-converting enzyme inhibitors, statins, and ezetimibe, as well as efforts to optimize anemia management, indices of bone-mineral disease, and fluid status. In the highrisk group, revascularization was done in 5 cases (63%), including 3 PTCAs with stents for single-vessel disease, and CABG for triple-vessel disease in 2 cases.

5. Discussion

The objective of this study was to gain understanding of survival and its modifying factors in transplant recipients at UD MHSC. To achieve this, I first validated an existing Spanish prognostic function on a group of patients grafted at UD MHSC Transplantation Center between 1991 and 15-09-2004; the function is used to estimate the risks involved in renal transplantation from a compound effect of various predictive factors. We assessed the calibration and discrimination performance of the function. We concluded that the function calibrated well in the low-risk group but it strongly overestimated mortality in the high-risk group. The function's discrimination performance is also poor. With this in light, the function we assessed cannot be used in clinical practice. Strong predictors identified both from the derivation and the validation dataset included pre-transplant cardiovascular disease (hazard ratio (HR) in our model: 2.5), vascular calcification (HR in our model: 2.2), and late graft function (HR in our model: 2.7). In our own dataset, length of time on dialysis prior to renal transplantation was found to be a less strong predictor. Several factors may explain the divergence of these results: different countries use different waiting list placement practices in assessing recipient suitability,

which results in a tendency where renal transplantation is given to kidney disease patients with lower cardiovascular risk and a lighter burden of co-morbidities. In a follow-up analysis of a French transplantation database on 1585 patients grafted between 2000 and 2004 at four centers, there was no difference in 5-year overall or kidney graft survival between preemptive vs off-dialysis renal transplantation, and a multiple Cox model identified no increased hazards of death or mortality-adjusted renal graft loss associated either with off-dialysis transplantation or with length of time on dialysis. The literature reports that post-transplant anemia is a significant, independent predictor of death and mortality-adjusted renal graft loss in kidney transplant recipients. Our study has also corroborated this. According to literature data, models estimating renal transplantation outcomes should undergo internal and external validation before clinical application. In building the function, attention must be paid to the number of predictors since over-parameterization with too many predictors may bias the results.

After adjustment for age and sex, we found no significant survival differences in patients who returned to dialysis. Graftectomy carried no survival benefit in the studied patients.

Screening for cardiovascular disease should be performed prior to renal transplantation as it has been known since an

analysis by Foley that cardiac mortality in dialysis patients is 10 to 20 times greater than in the average population. Cardiac mortality may be reduced to as low as a fraction of this level after successful renal transplantation but it still remains at 3 to 5 times above the reference range of the average population. In the majority of asymptomatic dialysis patients, coronary artery stenoses of 40 to 50% are found with no intervention following such findings. Aggressive risk reduction is warranted in these cases (ACEI, BB, statins, antiplatelet therapy). High-risk patients must be identified. Stress tests suitable for dialysis patients include stress echocardiography and myocardial perfusion imaging (scintigraphy). High-risk patients may skip these steps and require revascularization (intervention, cardiac surgery).

6. Novel findings

We described the survival of a group of patients grafted at UD MHSC Transplantation Center between 1991 and 15-09-2004. I validated an existing Spanish prognostic function for the first time on Hungarian patients. Strong predictors identified both from the derivation and the validation dataset included pre-transplant cardiovascular disease (hazard ratio (HR) in our model: 2.5), vascular calcification (HR in our model: 2.2), and late graft

function (HR in our model: 2.7). In our own dataset, length of time on dialysis prior to renal transplantation was found to be a less strong predictor.

After adjustment for age and sex, we found no significant survival differences in patients who returned to dialysis. Graftectomy carried no survival benefit in the studied patients. This conclusion is adaptable also to clinical practice. Preservation of the graft as long as possible is a reasonable recommendation: by gradual withdrawal of immunosuppression, graft rejection can be avoided and donor-specific antibody titer elevation can be prevented, since the intact graft will bind antibodies like a "sponge"; EPO resistance may also develop with malnutrition-inflammation syndrome and consequential anemia, which might affect success rates of further transplantations.

Cardiovascular screening when patients are placed on the waiting list is indispensable. In order to reduce early postoperative mortality, aggressive risk reduction and intervention specific to individual risk groups is recommended prior to transplantation, respectively.

7. Summary

My work involved the validation of a published Spanish prognostic function for the first time on Hungarian kidney transplant recipients. My work has confirmed that such functions require validation before clinical use because there is no guarantee that they will deliver good performance in patient populations other than their derivation dataset. The clinical applicability of the studied function is highly limited. In addition to published factors, we also assessed the role of other predictors. Beyond the predictors not originally included in the model but assessed in our investigation (sex, CIT, HLA match, body mass index, hemoglobin level), hemoglobin level was the only one to show a statistical significant association with survival.

More and more patients return to dialysis after renal transplantation due to graft failure. These patients have a poorer quality of life and their mortality is increased in the first year after returning to dialysis. When graft failure develops within one year

after transplantation, graftectomy is recommended. In cases when graft failure evolves after more than one year and the patient is suitable for further transplantation, we recommend keeping the graft with a stepwise withdrawal of immunosuppressive therapy. Adjusted for sex and age, survival in our patients returning to dialysis due to graft failure was no different than that in non-transplanted dialysis patients.

Cardiovascular screening of patients placed on the waiting list is paramount since the incidence of acute cardiac events rises in the first three months post-transplant, and cardiovascular disease is a leading cause of death on the long term in these patients. We aimed to reduce classic risk factors in all three risk groups (low, medium, high risk) of our patients; we optimized their cardioprotective medications and recommended their revascularization procedures to be scheduled before transplantation whenever possible. By timely management of modifiable clinical factors towards their optimal target values, reduction of time spent on dialysis and the correction of anemia in kidney transplant recipients, the life expectancy of kidney transplant recipients can be improved.

Key words: renal transplantation, prognosis, function validation, graft failure, cardiovascular screening

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List of publications related to the dissertation

1. **P. Szabó, R.**, Varga, I., Balla, J., Zsom, L., Nemes, B.: Cardiovascular Screening and Management Among Kidney Transplant Candidates in Hungary.
   Transplant. Proc. 47 (7), 2192-2195, 2015.
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List of other publications

4. Illésy, L., Kovács, D. Á., **P. Szabó, R.**, Asztalos, L., Nemes, B.: Autosomal Dominant polycystic Kidney Disese transplant Recipients After Kidney Transplantation: a single-center experience.
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